

## Clinical implications

- Idiopathic preterm delivery is the most important cause of perinatal mortality and morbidity
- No effective means exist to predict and prevent idiopathic preterm delivery
- This study found that about 15% of pregnant women have abnormal vaginal flora in the form of bacterial vaginosis in early pregnancy
- Women with bacterial vaginosis have fivefold increased risk of late miscarriage or preterm delivery
- Intervention studies are required to determine whether intervention can prevent a woman with bacterial vaginosis having a late miscarriage and preterm delivery

## HUMAN AND FISCAL COSTS

In the United States in 1980 it was estimated that the cost of neonatal intensive care exceeded \$460m. If all babies had been born healthy at term, it was estimated that this cost would have fallen to \$50m. The social and emotional cost of perinatal mortality and morbidity associated with preterm birth is immeasurable. If this treatment is successful it could lead to an overall reduction in the rate of late miscarriage and preterm birth of 30-40% with the associated reduction in the social, emotional, and economical costs. Treatment should be instituted no later than 16 weeks, if possible, to allow prevention of late miscarriage as well as preterm delivery. We are now undertaking a randomised double blind, placebo controlled antibiotic trial along such lines.

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## Blood pressure in prospective population based cohort of newborn and infant twins

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### Abstract

**Objective**—To describe blood pressure in twins during infancy.

**Design**—Prospective study of cohort of twins.

**Setting**—Teaching hospital in Florida.

**Subjects**—166 viable twin pairs born between July 1976 and December 1989.

**Main outcome measures**—Blood pressure and body weight at birth, at 14 days, and at 1, 3, 6, 9, and 12 months.

**Results**—Both systolic and diastolic pressure correlated with body weight throughout infancy (at birth  $r = 0.41$ ,  $P < 0.001$  and  $r = 0.42$ ,  $P < 0.001$  respectively; at 1 year  $r = 0.23$ ,  $P < 0.001$  and  $r = 0.26$ ,  $P < 0.001$  respectively). In infants weighing  $< 1500$  g at birth mean blood pressure rose from about 45/25 mm Hg to 101/55 mm Hg from birth to the age of 1 year, while in infants weighing  $> 3000$  g at birth it rose from 63/39 mm Hg to 100/61 mm Hg; corresponding mean body weights at 1 year were 7.86 kg and 9.88 kg. Differences in birth weight within pairs of monozygotic twins were negatively correlated

with such differences in systolic blood pressure at 1 year ( $r = -0.37$ ,  $P < 0.01$ ).

**Conclusions**—Blood pressure and body weights in twins showed strongly positive but generally declining correlations throughout infancy. Twins of lower birth weight showed a more rapid rate of rise in blood pressure during infancy. At 1 year the catch up in blood pressure exceeded that in body weight. Greater differences in birth weights between monozygotic twins were associated with smaller differences in systolic blood pressure at 1 year, suggesting that intrauterine environmental factors related to birth weight are important in determining blood pressure in infancy.

### Introduction

Technological advances over the past 20 or so years have improved the accuracy of non-invasive measurements of infant blood pressure. Many investigations have used these techniques to describe blood pressure among infants.<sup>1-12</sup> Data on newborn and infant twins,

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however, are sparse. To provide further understanding of blood pressure in twins during infancy, while avoiding bias in assembly of the series, we identified a population based cohort of twins and reported that significant genetic variance in blood pressure, body weight, and body length was detectable in early infancy.<sup>13-15</sup> Subsequent studies from Sweden,<sup>16</sup> the United Kingdom,<sup>17-21</sup> and Israel<sup>22</sup> found positive relations between low birth weight and hypertension in adulthood, and at least one study in animals found similar results.<sup>23</sup> In contrast, no association was found in young men from the United States.<sup>24</sup> In assessing the link between low birth weight and hypertension in adulthood it is also of interest to see whether the effects of prenatal environment on birth weight and blood pressure are detectable early in life. Our data from a total population cohort of newborn twins followed up prospectively allowed us to address this important and timely issue.

### Subjects and methods

All twin births at the Jackson Memorial Hospital at the University of Miami Medical Center over a period of 42 months were identified at delivery. Exclusion criteria included death or stillbirth of one twin (50 pairs) or severe illness in one twin (five pairs with hydrocephalus and three with multiple congenital anomalies). Of 222 eligible pairs, 38 were excluded because their parents refused permission to participate. Of the 184 (85%) pairs who were eligible and willing to participate, 14 dropped out because they moved from the state of Florida during the first year of life and four were lost to the study; follow up was therefore 90% complete (166/184). Data were collected in the newborn period; at 14 days; and at 1, 3, 6, 9, and 12 months. Complete follow up data were obtained on the 166 pairs at 1134 out of 1162 scheduled visits (98%).

### EXAMINATIONS

Methods of assessing zygosity, the number of chorions, placental cross circulation, the fetal twin-twin transfusion syndrome, and gestational age were performed as previously described.<sup>13</sup> Birth weight was taken from the records of the newborn nursery. At subsequent visits weights were obtained with study scales calibrated quarterly; infants were undressed before being weighed.

Blood pressure was measured with the Arteriosonde 1010 (Hoffman La Roche). Cuff size was one half to two thirds of the length of the right upper arm; pressure measurements were obtained with the cuff at heart level when the infant was quiet. For logistic rather than physiological reasons infants were supine during all measurements. Diastolic blood pressure was recorded as the point at which muffling occurred. The means of two blood pressure measurements obtained five minutes apart were used in the analyses. Quality management protocols from the United States National Heart, Lung, and Blood Institute were followed to produce quarterly assessments. Specifically, all observers measured 20 infants in the newborn nursery on a yearly basis. Infants were randomly selected, as was the sequence in which each observer measured the infant. Analysis of variance showed no significant differences between observers.<sup>25</sup> For the other quarterly checks observers were evaluated against a standardised video recording; films of descending mercury columns with accompanying Korotkoff sounds were shown and the blood pressures recorded by the observers were checked against the given set of correct answers.

### DATA ANALYSIS

A *t* test, based on among pair mean squares, was used to compare mean values instead of a *t* test. As

recommended by Christian and Norton,<sup>26</sup> we used the *t*' test because two groups of pairs rather than two groups of individuals are being compared. To adjust for possible confounding effects, we performed sex specific regression analyses of blood pressure on the sum of body weight and weight squared, and used the residual values as the basic unit of analysis.<sup>25</sup> Analysis of variance was used to assess the relative contribution of body weight and gestational age to blood pressure.<sup>25</sup> Pearson product moment coefficients were used to estimate the correlation of values at different points in time; analogous coefficients for within pairs of monozygotic twins were used to obtain correlation estimates controlled for genotype.<sup>25</sup>

### Results

Of the 166 twin pairs, 67 were monozygotic and 99 were dizygotic. Thirty seven of the monozygotic pairs were monochorionic and 27 dichorionic. In three cases the number of chorions could not be determined. Placental cross circulation was found for 31 of 35 monochorionic twins by dye injection, although only one case of the fetal cotwin transfusion syndrome was diagnosed (in two cases chorionicity was undetermined). Forty three monozygotic pairs were black, 23 white, and one Asian; 35 were boys and 32 girls. Of the dizygotic twins, 74 pairs were black, 24 white, and one Asian; 18 were both boys, 30 were both girls, and 51 one boy, one girl.

*t*' Tests showed no significant differences in systolic or diastolic blood pressure for zygosity (monozygotic pairs compared with dizygotic pairs), the number of chorions (monochorionic compared with dichorionic), placental cross circulation (present compared with absent), or race (white compared with non-white). Boys had somewhat higher values than girls; however, regression analysis indicated that the effect of sex was not independent of body weight. As such, values for the entire population were used to compile the mean (SD) values shown in figure 1. This figure depicts blood pressure at birth; 14 days; and 1, 3, 6, 9, and 12 months. Mean systolic pressure increased from 63 (10) mm Hg in the newborn period to 98 (10) mm Hg at 3 months and 102 (9) at 1 year. Corresponding values for mean diastolic pressure increased from 40 (9) mm Hg in the newborn period to 52 (10) at 1 year. Overall mean values for systolic and diastolic pressure at 6, 9, and 12 months were nearly identical (101/59, 100/59, and 101/59 mm Hg respectively).

Figure 2 shows mean systolic and diastolic blood pressure during the first year of life related to birth weight; table I shows gestational age and weight at 1 year according to birth weight. There was considerable overlap of gestational age for adjacent birth weight categories, and analysis of variance confirmed that gestational age did not exert a significant influence on either systolic or diastolic blood pressure independent of body weight. As infancy progressed mean blood pressure for each category of birth weight tended to become more alike. In part, this reflected a more rapid

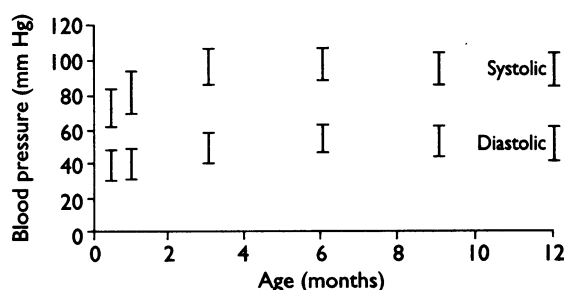


FIG 1—Mean (SD) systolic and diastolic blood pressures in 166 twin pairs from birth to 1 year

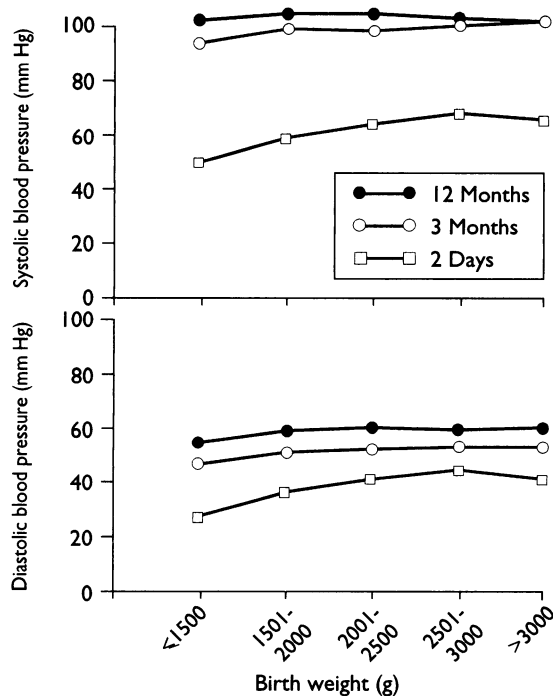


FIG 2—Mean systolic and diastolic blood pressures by birth weight in 332 twins at 2 days, 3 months, and 12 months

rate of rise in blood pressure during the first year of life experienced by low birthweight infants in this cohort. For example, the 20 infants weighing less than 1500 g at birth who had a mean systolic blood pressure about 2 SDs below that of the entire cohort at birth had a mean systolic blood pressure equal to that of the cohort as a whole by 1 year of age. The same pattern did not hold true for body weight, however.

Table II presents the correlations for weight and blood pressure at each age. The highest coefficients were found in the first month of life, but significant relations between body weight and both systolic and diastolic pressure were present at all ages. The pattern of decline in the correlation between blood pressure and body weight during infancy shown in table II is also seen in figure 2. For example, the mean blood pressure of the 20 infants whose birth weights were below 1500 g was similar to that of the cohort as a whole by 1 year of age, but mean body weight at 1 year remained substantially below that of the cohort as a

TABLE I—Gestational age and birth weight with weight at 1 year in 332 twins

	Birth weight (g)				
	≤ 1500 (n = 20)*	1501-2000 (n = 55)	2001-2500 (n = 110)	2501-3000 (n = 104)	> 3000 (n = 43)†
Gestational age (weeks):					
Mean	32 (1.8)	35 (2.0)	38 (1.8)	39 (1.3)	39 (1.1)
Range	30-37	30-38	33-42	36-42	36-42
Mean weight at 1 year (kg)	7.86	8.78	9.21	9.44	9.88

\*Includes one infant with birth weight < 1000 g.

†Includes three infants with birth weight > 3500 g.

TABLE II—Correlation coefficients (*r*) for blood pressure and body weight from birth to 1 year of age in 332 twins

Age	No of twins	Systolic blood pressure		Diastolic blood pressure	
		<i>r</i>	P value	<i>r</i>	P value
Newborn	326	0.41	< 0.001	0.42	< 0.001
14 Days	312	0.45	< 0.001	0.39	< 0.001
1 Month	326	0.55	< 0.001	0.49	< 0.001
3 Months	328	0.30	< 0.001	0.20	< 0.001
6 Months	330	0.30	< 0.001	0.27	< 0.001
9 Months	324	0.27	< 0.001	0.29	< 0.001
12 Months	330	0.23	< 0.001	0.26	< 0.001

whole. Among the lower birthweight infants, therefore, rates of catch up in body weight tended to be slower than the rates of catch up in blood pressure.

Controlling for genotype, we calculated correlation coefficients for differences within pairs among monozygotic twins. The correlation coefficient for such differences in birth weight and systolic blood pressure at 1 year ( $r = -0.37$ ,  $P < 0.001$ ) showed that monozygotic twins with greater disparities in birth weight tended to have lower disparities in blood pressure at 1 year. Differences within pairs in the ratio of weight at 1 year to birth weight and systolic pressure at 1 year of age were positively correlated ( $r = 0.39$ ,  $P < 0.001$ ), suggesting that the member of the pair with the greater difference in the ratio of weight at 1 year to birth weight had a greater difference in systolic blood pressure at 1 year. A significant negative correlation ( $r = -0.22$ ,  $P = 0.01$ ) was found for differences within pairs in weight and systolic blood pressure at 1 year, suggesting that the greater the difference in weight at 1 year the less the difference in systolic blood pressure at 1 year. Analogous coefficients for diastolic pressure were not significant.

Table III shows correlations for systolic and diastolic blood pressure at 1 year of age, with corresponding values from the newborn period to 9 months. The highest correlations ( $0.36$ ,  $P < 0.001$  and  $0.23$ ,  $P < 0.001$  for systolic and diastolic pressure respectively) were found between 9 months and 1 year, but significant correlations with values at 1 year were present as early as the newborn period for systolic pressure and by 14 days for diastolic pressure.

TABLE III—Correlation coefficients for blood pressure at two points in time (tracking correlations) in 332 twins

Time points	No of twins	Systolic blood pressure		Diastolic blood pressure	
		<i>r</i>	P value	<i>r</i>	P value
Newborn-1 year	324	0.13	0.020	0.10	0.070
14 Days-1 year	312	0.05	NS	0.13	0.020
1 Month-1 year	326	0.05	NS	0.12	0.026
3 Months-1 year	326	0.20	< 0.001	0.12	0.026
6 Months-1 year	328	0.30	< 0.001	0.20	< 0.001
9 Months-1 year	322	0.36	< 0.001	0.23	< 0.001

## Discussion

Our data show that mean blood pressure rose rapidly during the first weeks of life. In contrast, mean values for systolic and diastolic pressure were nearly identical at 6, 9, and 12 months. The data also show significant, although generally declining, positive correlations between body weight and blood pressure throughout infancy. Blood pressure in infants was, however, independent of gestational age, sex, race, zygosity, the number of chorions, and placental cross circulation. The twins with lower birth weights tended to have the most rapid rate of rise in blood pressure during infancy. Moreover, when genotype was controlled for by restricting analyses to monozygotic twins the twin pairs with greater disparities in birth weight tended to have smaller disparities in systolic blood pressure at 1 year. Blood pressure at 1 year correlated significantly with values in the newborn period for systolic pressure and at 14 days of life for diastolic pressure.

## COMPARISONS WITH SINGLETONS

Previous reports of blood pressure in infants have shown a wide range of values depending, in part, on the birthweight characteristics of the study populations. Reported perinatal values in studies of low birthweight singletons, for example, have been lower than almost all other reports dealing with perinatal blood pressure among heavier babies.<sup>9,11</sup> In our cohort more than half of the infants weighed less than 2500 g at birth, or

below the 10th centile at sea level, from the 38th week of gestation onwards.<sup>27</sup> Though the overall values in our newborn infants are lower than previously described,<sup>1 2 3 5 7 12</sup> they are more consistent with reported tendencies from populations of predominantly low birthweight singletons. For example, the values in newborn infants weighing < 1500 g are nearly identical with those reported by Spinazzola *et al* for very low birthweight singletons,<sup>11</sup> and values for newborn infants weighing 1501-2500 g are exactly within the ranges noted by Gennser *et al* for 1550-2500 g singletons.<sup>16</sup> The values for twins weighing 2500 g or more at birth are comparable with those we obtained for full term singletons followed up from birth to 1 year of age.<sup>1</sup> The similarity in the distribution of blood pressures at birth according to birth weight in twins and singletons may be particularly important in light of the values in 1 year old twins.

Blood pressures at 1 year in our cohort were generally higher than those in singletons.<sup>1 2 6 10 12</sup> We used a cuff size between one half and two thirds of the length of the upper arm. This is generally narrower than has been previously used and than the current recommendations (two thirds of the length of the upper arm).<sup>28</sup> This might have contributed to the higher values, but such an explanation would be inconsistent with the generally lower pressures found at birth because the same methods were used in each case. Interestingly, mean systolic blood pressure in the twins at 1 year is comparable with the mean value we obtained in singletons (101/63 mm Hg *v* 101/59 mm Hg for the twins.<sup>1</sup> Almost all of the singletons were of normal birth weight according to the same protocol and using the same equipment.<sup>1</sup> We might therefore conclude that intrauterine factors related to birth weight did not affect blood pressure in the twins except that body weight among the twins failed to catch up at the same rate as did blood pressure.

Specific evidence that intrauterine environmental factors related to birth weight did affect the development of blood pressure in our cohort is found in the correlations between within pair differences in systolic blood pressure and birth weight among monozygotic twins. As monozygotic twins have the same genotype, it follows, for example, that the greater degree of correspondence between systolic blood pressure at 1 year of age among twins with a greater disparity in birth weight ( $r = -0.37$ ,  $P < 0.001$ ) was related to intrauterine environmental determinants of birth weight.

#### COMPARISONS WITH OTHER STUDIES

In addition to the mean values depicted in figure 2, the greater rate of rise in blood pressure from birth to 1 year of age among infants in the lower birthweight categories of this cohort was also reflected by declining

correlations between blood pressure and body weight during the period of follow up. These observations are consistent with the pattern of generally declining correlations between blood pressure and body weight reported throughout infancy by de Swiet *et al*.<sup>12</sup>

Several studies, however, failed to find significant relations between infant blood pressure and body weight<sup>3 4 6-8 10 11</sup> and at least one found significant but increasing correlation coefficients from birth to the age of 1 year.<sup>2</sup> All of the study populations showing a poor correlation found a more homogeneous distribution of body weight than we did. The populations were low birth weight<sup>7 11</sup>; healthy, full term infants<sup>3 4 10</sup>; a moderately sized, community based cohort<sup>6</sup>; and completely healthy infants from various private and public clinics.<sup>8</sup> This may suggest that twin cohorts, because of their overrepresentation of low birthweight infants, are better for detecting subtle but potentially important interrelationships between blood pressure and body weight than more uniform, predominantly singleton populations. The correlation pattern between blood pressure and body weight in our study and that of the large, community based study by de Swiet *et al*<sup>12</sup> is consistent with this view because an average of 1391 predominantly singletons were seen at each visit in de Swiet *et al*'s study. The reported lower blood pressures in predominantly low birthweight infant populations may provide even stronger evidence that previous failure to detect correlations between blood pressure and body weight among infants represents  $\beta$  error. Uhari reported increasingly strong correlations between blood pressure and body weight in infancy, but 245 babies were examined on the first day, 224 on the fourth and fifth days, 105 at 4 months, and 68 at 1 year in this study.<sup>2</sup> This design does not reflect a longitudinal cohort follow up study so much as a series of cross sectional studies of an original cohort, which makes it difficult to interpret the observations longitudinally.

#### CONCLUSIONS

Because the prenatal environment of twins differs from that of singletons the association between intrauterine environmental factors that affect these twins' birth weight and their blood pressure during the first year of life might simply reflect one of the unique characteristics of twins—for example, placental cross circulation. This remains to be determined, however. For the moment, our observations on twins should be viewed in the context of several other factors which contribute to the totality of available evidence.

Firstly, blood pressure and body weight are related in our cohort and the large study of singletons by de Swiet *et al*.<sup>12</sup> Secondly, several reports from the United Kingdom support a relation between birth weight and blood pressure later in life,<sup>17-21</sup> and at least two reports from outside the United Kingdom also support this hypothesis.<sup>16 22</sup> Thirdly, such an association has also been reported in guinea pigs.<sup>23</sup> Fourthly, how particular maternal prenatal factors—for example, intakes of potassium and calcium—might affect blood pressure in offspring is unclear.<sup>29</sup> Therefore, the impact of such factors on previous estimates of possible associations between birth weight and blood pressure cannot be measured. Finally, the increase in risk for both low birth weight and hypertension among African-Americans may be coincidence, or pathobiological concordance.<sup>30</sup> If an association between low birth weight and hypertension is substantiated by future research it could prove highly important to the development of effective disease prevention strategies. Furthermore, detecting such a tendency early in life may provide enhanced opportunities to modify future risk. Our data suggest that additional studies of infant twins, as well as relation between birth weight and

#### Clinical implications

- Low birth weight is associated with the development of hypertension in adulthood
- In assessing this association it is interesting to see whether the effects of prenatal environment on birth weight and blood pressure are detectable in infancy
- This study found that both diastolic and systolic blood pressure correlated with body weight in infant twins throughout the first year of life, although to a declining extent
- Lower birthweight twins showed a more rapid rise in blood pressure during infancy such that at the age of 1 year the catch up in blood pressure exceeded that in body weight
- Large differences in birth weight among identical twins were associated with small differences in systolic pressure at the age of 1 year, which suggests that the intrauterine environment is important in determining blood pressure in infancy

blood pressure among adult twins, would be of interest.

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## Influence of sex, age, body mass index, and smoking on alcohol intake and mortality

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### Abstract

**Objective**—To examine the association between self reported alcohol intake and subsequent mortality from all causes and if the effect of alcohol intake on the risk of death is modified by sex, age, body mass index, and smoking.

**Design**—Prospective population study with baseline assessment of alcohol and tobacco consumption and body mass index, and 10-12 years' follow up of mortality.

**Setting**—Copenhagen city heart study, Denmark.

**Subjects**—7234 women and 6051 men aged 30-79 years.

**Main outcome measure**—Number and time of deaths from 1976 to 1988.

**Results**—A total of 2229 people died, 1398 being men. A U shaped curve described the relation between alcohol intake and mortality. The lowest risk was observed at one to six alcoholic beverages a week (relative risk set at 1). Abstainers had a relative risk of 1.37 (95% confidence interval 1.20 to 1.56) whereas those drinking more than 70 beverages a week had a relative risk of 2.29 (1.75 to 3.00). Among the drinkers, the risk was significantly increased only among those drinking more than 42 beverages a week. Sex, age, body mass index, and smoking did not significantly modify the risk function. The risk among heavy drinkers was slightly reduced when smoking was controlled for. The risk function was similar in the first and second period of six years of observation.

**Conclusion**—Alcohol intake showed a U shaped

relation to mortality with the nadir at one to six beverages a week. The risk function was not modified by sex, age, body mass index, or smoking and remained stable over 12 years.

### Introduction

The impact of alcohol intake on mortality has been described in several large prospective studies from different countries.<sup>1-11</sup> Apart from two studies,<sup>4,6</sup> they all showed that the curve describing the risk of death in relation to alcohol intake is U shaped. This may have new public health implications. Before making recommendations about alcohol intake, the stability of the risk function across sex, age, and other common and established health hazards should be evaluated. Alcohol intake as well as its effect on mortality may be related to sex and age.<sup>12</sup> Among the relevant health hazards are extreme body weight and smoking. Both body weight and smoking are correlated to alcohol intake.<sup>3,12-14</sup> Thinness, obesity, and smoking are associated with increased mortality.<sup>15,16</sup>

We assessed the relation between alcohol intake and risk of dying and took into account sex, age, body mass index, and smoking habits and estimated the impact on the population mortality.

### Subjects and methods

#### POPULATION

The study population comprised a random, age stratified sample of 19 698 people out of 87 172 aged 20

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